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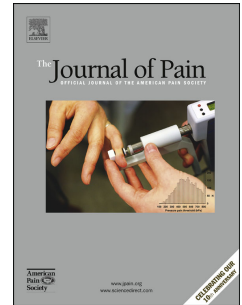
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Beliefs about pharmaceutical medicines and natural remedies explain individual variation in placebo analgesia

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Abstract

This study examined whether placebo responses were predicted by a theoretical model of specific and general treatment beliefs. Using a randomised cross-over, experimental design (168 healthy individuals) we assessed whether responses to a cold pressor task were influenced by two placebo creams described as Pharmaceutical vs Natural origin. We assessed whether placebo responses were predicted by pre-treatment beliefs about the treatments (placebo) and by beliefs about the pain. The efficacy of both Pharmaceutical and Natural Placebos in reducing Pain Intensity was predicted by aspects of pain catastrophizing including Feelings of Helplessness (Pharmaceutical: $B=0.03$, $p<0.01$, Natural: $B=0.02$, $p<0.05$) and Magnification of Pain (Pharmaceutical: $B=0.04$, $p<0.05$, Natural: $B=0.05$, $p<0.05$) but also by pre-treatment Necessity beliefs (Pharmaceutical: $B=0.21$, $p<0.01$, Natural: $B=0.16$, $p<0.05$) and, for the Pharmaceutical condition, by more general beliefs in personal sensitivity to pharmaceuticals ($B=0.14$, $p<0.05$). Treatment Necessity beliefs also partially mediated the effects of Helplessness on placebo responses. Treatment Necessity beliefs for the Pharmaceutical Placebo were influenced by general pharmaceutical beliefs whereas Necessity beliefs for the Natural Placebo were informed by general background beliefs about holistic treatments. Our findings demonstrate that treatment beliefs influence the placebo effect suggesting that they may offer an additional approach for understanding the placebo effect.

Perspective: Placebo effects contribute to responses to active analgesics. Understanding how beliefs about different types of medicines influence placebo analgesia may be useful in understanding variations in treatment response. Using the cold-pressor paradigm we found that placebo analgesia is influenced by beliefs about natural remedies, pharmaceutical medicines and about pain.

Key words:

- Treatment beliefs
- Placebo effect
- Pharmaceutical medicines
- Natural remedies
- Analgesia

1. Introduction

Placebo effects are thought to be influenced by beliefs. These are usually operationalised as treatment expectations but are other beliefs also important? Horne and colleagues have developed a theoretical model for the origin and effects of beliefs about pharmaceuticals [14]. The model differentiates between specific and general beliefs. Specific beliefs pertain to a particular medicine and are often operationalised as how the individual judges their personal need for the treatment (necessity beliefs), relative to their concerns about potential harms [15; 16].

Specific treatment evaluations are related to more general 'background' beliefs or pharmaceutical schema comprising ideas about medicines as objects (e.g. the degree to which they are generally harmful, beneficial, overused by doctors etc. [20]) and beliefs about self in relation to medicines (e.g. beliefs about personal sensitivity to medicines [17]). In representations of pharmaceuticals, their harm is often linked to their essence as manufactured 'chemicals', in contrast to 'natural' remedies that are perceived more positively [14]. Negative pharmaceutical schemas are often associated with more positive beliefs about natural remedies [9; 14].

The anticipated relationship between specific and general beliefs about treatment can be represented by the theoretical model shown in Figure 1. This model is derived from observations that specific treatment beliefs such as treatment necessity are influenced by more general background beliefs about treatment i.e. pharmaceutical schema [7; 19], but also by representations of the condition being treated [22]. In situations where treatment is prescribed to reduce pain, treatment necessity beliefs are likely to be related to perceptions of the pain (e.g. pain severity ratings) and to related cognitions such as pain catastrophizing (see Figure 1) [34; 36].

Figure 1: Hypothesised relationship between beliefs about pain, general treatment beliefs, treatment necessity and the placebo effect.

In this study we examine whether our model of treatment representations can explain variations in the placebo effect. To do this we prepared two (deceptive) placebo creams that were differentially described as having pharmaceutical vs a natural origin. This enabled us to examine whether responses to the placebo (e.g. reduction in pain scores) were related to specific beliefs and general beliefs about the treatments.

We will test the following hypotheses:

Hypothesis 1: Variation in placebo responses in both conditions will be predicted by the participant's Specific Necessity beliefs (i.e. their perception of personal need for the specific 'treatment' pharmaceutical vs. natural).

Hypothesis 2: High pain catastrophizing will be associated with stronger Necessity beliefs and a larger placebo effect.

Hypothesis 3: Specific Necessity will be differentially influenced by general pharmaceutical schema and general beliefs about complimentary medicine. More positive pharmaceutical schema will be associated with stronger beliefs in the necessity for the Pharmaceutical Placebo and more positive beliefs in complementary and natural medicine with stronger beliefs in the necessity for the Natural Placebo.

Hypothesis 4: Negative pharmaceutical schema will be associated with more positive beliefs about complementary and natural remedies and preferences for this type of treatment.

2. Method

This study was approved by the UCL Ethics Committee (ref: 4875/002). The study had a within-subject crossover design. Participants attended a single testing session in which they completed 3 conditions in a random order: Pharmaceutical Condition, Natural Condition and No Placebo Condition.

2.1. Sample and recruitment procedure

The sample size was calculated using G Power (G*Power v3.1.9.2), for testing a linear multiple regression model (fixed, R^2 increase), 80% power and an alpha error probability of 0.05. We calculated the required sample size based on a study which reported that expectations explained 7.3% of the variance in cold pressor pain severity [35]. A sample size of 168 was required in order to explain a total variance of 7.3% by 5 predictor variables of interest (Necessity, Concerns, General Benefit, General Harm and PSM) in a multiple regression model.

Participants were invited to take part in a study comparing the effectiveness of two new pain-relieving creams via the UCL Announcement Email Service between June and December 2014. Participants were included if aged 18 years and above, and able to sufficiently understand spoken and written English. Participants were excluded if they reported a history of the following medical conditions: fainting/seizures, cardiovascular disease, circulation

disorders, or if they had the following conditions in the past two weeks: chronic pain, back pain, severe headaches, and arthritis or hand injuries. Participants were also excluded if they were currently taking medication for pain, anti-depressants or sedatives. Potential participants were emailed the information sheet and a screening questionnaire to check eligibility and given at least 24 hours to decide whether to participate. Informed consent was obtained on the day of the experiment. Participants were paid £10 for their time. The experiment took 1 hour to complete.

2.2. Measures

Sociodemographics

We asked participants to provide their age in years, gender, ethnicity, current qualification they were studying (undergraduate or postgraduate degree) and first language.

Treatment Beliefs

1. *Pharmaceutical Schema and general Treatment Beliefs*

Beliefs about Medicines Questionnaire – General (BMQ-G) [20]

The BMQ-G consists of 3 scales: a 4-item scale assessing beliefs about the benefit of medicines in general (General Benefit; e.g. '*Medicines help many people to live better lives*'), a 5-item scale assessing their capacity to cause harm (General Harm; e.g. '*All medicines are poisons*') and a 3-item scale assessing their overuse by doctors (General Overuse; e.g. '*Doctors use too many medicines*'). All items were scored on a 5-point Likert-type scale (1=strongly agree, 2=disagree, 3=uncertain, 4=agree, 5=strongly agree). A scale-adjusted mean score for each scale was computed by dividing the mean scale score by the number of items. All 4 scales have been validated [17] and had adequate reliability in the current sample (General Benefit $\alpha = 0.55$, General Harm $\alpha = 0.64$, General Overuse $\alpha = 0.67$).

Perceived Sensitivity to Medicines (PSM) [17]

The PSM is a 5-item scale assessing beliefs about personal sensitivity to the effects of medicines (e.g. '*My body is very sensitive to medicines*'). All items were scored on a 5-point Likert-type scale (1=strongly agree, 2=disagree, 3=uncertain, 4=agree, 5=strongly agree). A scale-adjusted mean score for each scale was computed by dividing the mean scale score by the number of items. The PSM has been validated [17] and had adequate reliability in the current sample ($\alpha = 0.78$).

Complementary and Alternative Medicines Belief Inventory (CAMBI) [2]

The CAMBI measures Beliefs about Complementary and Alternative Medicine. It has four 5-item subscales measuring beliefs about: Holistic Health (health and illness involve the whole person e.g. “Health is about harmonizing your body, mind and spirit”); Holistic Treatments (treatment should focus on the body’s healing mechanisms e.g. “It is important for treatments to boost my immune system”); Natural Treatments (natural treatments are safer than orthodox medicines) e.g. “Treatments should only use natural ingredients”; and Participation in Treatment (patients should be actively involved in their treatment). Items were scored on a 7-point Likert-type scale (0=strongly disagree, 7=strongly agree). Scores for each item were summed to produce a total score for each scale. This questionnaire has shown good validity [2]. The Holistic Health, Holistic Treatment and Natural Treatment scales had adequate to good internal consistency in our sample ($\alpha = 0.59, 0.61, 0.49$ respectively). The Participation in Treatment scale had poor internal consistency ($\alpha = 0.28$) and so was not used in the analysis.

2. *Specific beliefs about the placebo cream (Beliefs about Medicines Questionnaire – Specific Scale; BMQ-S) [20]*

The BMQ-Specific was used to assess perceptions of the ‘pain-relieving’ cream. It comprises two scales: a 5-item Necessity scale assessing perceptions of personal need for the cream and a 6-item Concerns scale assessing concerns about potential negative effects of the cream. The BMQ-S was developed for examining beliefs about medicines prescribed for those with ongoing health issues. As our sample were healthy individuals experiencing experimentally induced pain we modified each item to apply to this setting (see Table 1). Items were scored on 5-point Likert-type scales (where 1=strongly agree, 5=strongly agree). A scale-adjusted mean score for each scale was computed by dividing the mean scale score by the number of items. Both scales had good internal consistency in both conditions (Pharmaceutical Condition: Necessity $\alpha = 0.61$, Concerns $\alpha = 0.71$, Natural Condition: Necessity $\alpha = 0.68$, Concerns $\alpha = 0.64$).

3. Treatment preference

Participants were asked to choose which cream they would use if they were suffering from muscle pain.

Pain Catastrophizing Scale (PCS) [34]

The PCS is a 13-item questionnaire measuring propensity to exaggerate the seriousness or threat value of pain. It can be divided into 3 subscales measuring Rumination (e.g. "I can't stop thinking about how much it hurts"; PCS-Rumination), Magnification of Pain (e.g. "I worry that something serious may happen"; PCS-Magnification), and Feelings of Helplessness (e.g. "It's awful and I feel that it overwhelms me"; PCS-Helplessness) during pain.

Participants indicate the degree to which they have these thoughts and feelings using a 5 point scale (0=not at all, 4=all the time). Totals for each subscale are calculated by adding scores from each item. This questionnaire has been validated [27] and had good internal consistency for all 3 subscales (PCS–Rumination $\alpha = 0.75$, PCS–Magnification $\alpha = 0.85$, PCS–Helplessness $\alpha = 0.59$).

Expectations of drug efficacy and Pain Intensity (VAS)

Visual Analogue Scales (VAS) were used to measure expectations of drug efficacy (Efficacy Expectations: 0 = Not effective at all, 100 = Highly effective), and Expected Pain Intensity (0 = Least possible pain, 100 = Worst possible pain).

Patient Health Questionnaire – 9 (PHQ-9) [21]

The PHQ-9 is a 9-item screening assessment for depression severity. Participants indicated how bothered they had been about 9 features of depression, over the past 2 weeks (e.g. "Little interest or pleasure in doing things"). Items were scored on a 4-point Likert-type scale (0=not at all, 1=several days, 2=more than half the days, 3=nearly every day). A total score was calculated by summing item scores. It has been validated in clinical and general populations [21; 23], and had good internal consistency ($\alpha = 0.87$).

State Trait Anxiety Inventory – Trait (STAI-T) [32]

This 20-item questionnaire was used to measure Trait Anxiety. For each item, participants rated how they generally feel (e.g. "I feel nervous and restless") using a 4-point scale (1=almost never, 4=almost always). A total score was calculated by adding scores from each item. It has shown good validity [32] and had good internal consistency ($\alpha = 0.75$).

Positive and Negative Affect Schedule - State (PANAS) [40]

State Affect was measured using the PANAS, which consists of two 10-item scales measuring Positive Affect and Negative Affect. Both scales showed good internal consistency for all 3 conditions (Pharmaceutical Condition: Positive Affect $\alpha = 0.91$, Negative Affect $\alpha = 0.85$, Natural Condition: Positive Affect $\alpha = 0.93$, Negative Affect $\alpha = 0.83$, No Placebo Condition: Positive Affect $\alpha = 0.93$, Negative Affect $\alpha = 0.83$). Participants indicated how they are feeling at that moment (e.g. “Interested”, “Scared”) using a 5-point scale (where 1= very slightly or not at all, to 5 = extremely). Scores for each scale were calculated by adding each item score.

Pain Tolerance

Pain Tolerance was measured by timing how long participants left their hand submerged in the water bath. Pain Tolerance was defined as the time from immersion to withdrawal of the hand from the water.

Short-Form McGill Pain Questionnaire (SF-MPQ) [24]

The SF-MPQ measures Pain Intensity using a visual analogue scale (VAS, 0 = Least possible pain, 100 = Worst possible pain), and Multidimensional Pain Intensity scale (MPQ) using 11 items assessing sensory pain and 4 items assessing affective pain. For each MPQ item, participants rated how much of that quality (e.g. sharp) their pain had from 0 =none to 3 = severe. The scale showed good internal consistency for each condition (Pharmaceutical Condition $\alpha = 0.85$, Natural Condition $\alpha = 0.84$, No Placebo Condition $\alpha = 0.81$). Total scores for each scale were calculated by adding the score from each item. Participants also completed the Present Pain Intensity measure (PPI) where they are asked to rate their overall pain intensity from 0 = no pain to 5 = excruciating.

Side Effect Frequency

Participants were provided with a list of 6 common side effects to pain medication – Skin Irritation, Headache, Nausea, Dizziness, Fatigue, Hot flushes and were asked to report if they had experienced them or not. They were also provided with the option to note any other side effects they had experienced.

Manipulation Checks

Participants were asked to state what they thought the aim of the study was. Finally using a VAS, they were asked whether they thought they had received a placebo or an active medication for each condition (where 0=placebo and 100=active medication).

2.3. Conditions

In the Natural and Pharmaceutical Conditions participant were presented with patient information leaflets describing each 'treatment' (see Figure 2 and 3). Side effect information was not provided to participants in the Natural and Pharmaceutical Conditions. In the No Placebo Condition participants were provided with the following message: *"The purpose of this condition is to compare normal pain severity/tolerance against the condition where you will receive a medicine to see how effective the drugs are in reducing pain"*.

Figure 2: Patient information leaflet for the Pharmaceutical Placebo.

Figure 3: Patient information leaflet for the Natural Placebo.

2.4 Cold pressor task

The temperature of the water bath (Julabo F-12 Refrigerated Circulator) was set at 2°C [5]. Participants were instructed to submerge their hand in the water up to their wrist for as long as possible (maximum 2 minutes). The experimenter remained out of view during this task to reduce any audience effects from influencing results.

2.5. Filler task

Between each condition, participants were asked to complete a 'Magic Square' task to keep them engaged while their hand re-acclimatised to normal temperature. The task involved a 3x3 grid where they were required to place numbers from 1-9 in each square so that each row column and diagonal adds up to 15 [31]. Participants were told that this task was to test their cognitive abilities after experiencing pain and to complete it within 5 minutes.

2.6. Procedure

Participants first completed the Baseline Measures (Sociodemographics, BMQ-G, PSM, CAMBI, PHQ-9, STAI-T, and PCS). Then they were exposed to each condition in a randomized order. Hand order (dominant – non-dominant - dominant hand or vice versa) was also randomized. Randomisation was determined for each participant using an online randomiser (unblind, using www.randomizer.org) before participants came in for the experiment and they were not told the order of conditions. In each condition, participants read the Condition-Specific Message, then the completed the Condition-Specific Measures (BMQ-S, PANAS and Expectations) and the cold pressor task. Pain Tolerance was

measured during each cold pressor task. Immediately after the task participants completed the Post-Cold Pressor Measures (SF-MPQ, Side Effects). Between each condition participants completed the filler task.

Once all conditions had been completed, participants completed the Manipulation Checks. Finally, participants were fully debriefed (see Figure 4).

Figure 4: Overview of procedures. BMQ-G = Belief about Medicines Questionnaire – General, PSM = Perceived Sensitivity to Medicines, CAMBI – Complementary and Alternative Medicines Belief Inventory, PHQ-9 = Patients Health Questionnaire – 9, STAI-T = State Trait Anxiety Inventory – Trait, Pain Catastrophizing Scale, PANAS, Positive and Negative Affect Schedule, BMQ-S = Beliefs about Medicines Questionnaire – Specific, SF-MPQ = Short Form McGill Pain Questionnaire.

2.7. Statistical analysis

Analyses were used to address the following questions/hypotheses:

Descriptive statistics

Baseline measure scores were dichotomized at either the scale mid-point or at the median score for descriptive purposes

Was the placebo cream convincing?

Paired t-tests were performed to determine if there were significant differences in Expected Efficacy, Expected Pain Intensity, Necessity and Concerns, Pain Intensity (VAS, MPQ, PPI), and Pain Tolerance across conditions. Scores for the BMQ-S subscales were dichotomized at the scale mid-point to describe participants as high or low on each subscale. Scores for Necessity and Concerns in the Natural Condition were subtracted from the Pharmaceutical Condition to determine whether participants formed different perceptions about the placebo cream in each condition.

Did we observe a placebo effect?

Repeated-measures ANOVA was used to determine whether a significant placebo effect was observed in response to the Pharmaceutical and Natural Placebo (MPQ, VAS and OPI Pain Intensity, and Pain Tolerance).

Hypothesis 1: Variation in placebo responses in both conditions will be predicted by the participant's Necessity beliefs.

The placebo effect for Pain Intensity (MPQ, VAS and PPI Placebo Effect) and Tolerance

(Tolerance Placebo Effect) were calculated by subtracting scores obtained in the Pharmaceutical and Natural Conditions from the No Placebo Condition. We employed multiple linear regression to determine whether Necessity beliefs predicted variations in placebo analgesia in each condition. We used the placebo effect derived from the MPQ scale (MPQ Placebo Effect) as our primary outcome measure for Pain Intensity as it is a multidimensional measure of pain. Secondary outcome measures included VAS, OPI and Tolerance Placebo Effect. In addition to this, we also examined the effect of other specific treatment beliefs (specific concerns), participants' Pharmaceutical Schemas (General Benefit, Harm and Overuse, PSM), Beliefs about CAM (CAMBI: Natural Treatments, Holistic Treatments, Holistic Health) and Expectations (Efficacy Expectations and Expected Pain Intensity) on placebo analgesia in each condition.

Hypothesis 2: High pain catastrophizing will be associated with stronger Necessity beliefs and a larger placebo effect.

We then tested the effects of Pain Catastrophizing on the placebo effect for each condition using multiple linear regression. A Sobel test determined whether any effect of beliefs about the impending pain (Pain Catastrophizing) on the placebo effect was mediated by Necessity. Finally we included significant predictors in a regression model to determine the overall variance of the placebo effect by these variables.

Hypothesis 3: Specific Necessity will be differentially influenced by general pharmaceutical schema and general beliefs about complimentary medicine.

Pearson's correlations were conducted to examine relationships between general beliefs about medicines, PSM, Specific Beliefs about the placebo and Beliefs about CAM. A binomial test was used to determine whether there was a significant preference for either the Natural or Pharmaceutical Placebo within our sample. Independent t-tests were conducted to determine significant difference in treatment beliefs, beliefs about CAM and Pain Intensity in response to each placebo between those who preferred to use the Natural vs. Pharmaceutical Placebo. Analyses were conducted using IBM SPSS Statistics v21.

3. Results

3.1. Sample characteristics

Of 236 individuals who expressed interest, 21 did not meet the inclusion criteria. Of the 215 who agreed to take part after screening, 47 did not attend their appointment and 168 attended and completed the experiment. The mean age of these participants was 25.69

years with the majority being female (63.70%). Just over a third of participants were currently studying an undergraduate degree with the rest studying for a postgraduate degree. Most participants spoke English as their first language (see Table 2).

3.2. Baseline Measures

Pharmaceutical schema and general beliefs about medicines

Most participants expressed positive views about pharmaceutical medicines. All but one participant (99.40%) had high General Benefit beliefs, scoring above the scale mid-point (mean = 3.98 SD = 0.45). The majority of our sample viewed medicines as generally safe (Low General Harm 81.50%, mean = 2.24 SD = 0.59) and had low PSM (93.50%, mean = 2.05 SD = 0.58), scoring below the scale mid-point. However, two thirds of our sample believed that medicines are over prescribed by doctors, scoring above the scale mid-point (66.70%, mean = 3.06 SD = 0.69). Mean scores for the CAMBI – Natural Treatment, Holistic Treatment and Holistic Health scales were 17.45 (SD = 4.51), 20.65 (SD = 3.86) and 15.38 (SD = 3.81), respectively. These scores were around the scale midpoint suggesting participants were ambivalent to whether medication should be natural, utilize the body's own mechanisms, and focus on the body "as a whole".

State/Trait Psychological Variables

A median Depression score of 3 (IQR = 6) was observed with 18.5% of our sample scoring above the criteria for depression severe enough to warrant medical intervention. Mean scores for PCS – Rumination, Magnification and Helplessness were 5.24 (SD = 3.90), 2.43 (SD = 1.99) and 4.90 (SD = 3.98) suggesting participants generally were low pain catastrophizing tendencies (scoring below the scale mid-point). Finally a mean Trait Anxiety score of 43.18 (SD = 6.49) was observed suggesting moderate levels of Trait Anxiety within our sample (see Table 3).

3.3. Was the placebo cream convincing? Manipulation check and side effect reports

We conducted paired t-tests to determine whether participants tended to have different beliefs and expectations about the Natural and Pharmaceutical Placebos. Regardless of whether the treatment was described as Pharmaceutical or Natural, Mean Necessity beliefs in each treatment condition were above the scale mid-point, indicating that most participants felt that they needed the treatment, while Concerns were low, with a mean below the scale mid-point. Necessity beliefs were significantly greater in the Pharmaceutical Condition

compared to the Natural Condition (mean difference score = 0.19 SD = 0.54) (see Table 4). Concerns about its adverse effects were also typically higher for the Pharmaceutical cream than the Natural cream (mean difference score 0.20, SD = 0.50). However, there was variation in how participants perceived the placebos, with some participants having higher Concerns and higher perceived need for the Natural cream (see Figure 5).

Figure 5: Frequency distributions for Necessity (left) and Concerns (right) difference scores.

Participants expected less pain from the cold pressor task when they were given the cream (Pharmaceutical and Natural Conditions) than when they were not given a cream (No Placebo Condition). There was not a significant difference in expected pain between the Natural and Pharmaceutical Conditions. Overall, participants expected the Pharmaceutical Placebo to be more effective than the Natural Placebo (see Table 4).

Most of our participants believed that the cream was, or could be an active drug; only 6 of our 168 participants thought the cream was definitely a placebo (Pharmaceutical Condition: mean = 51.90, SD = 23.77, Natural Condition: mean = 51.39, SD = 25.21). Furthermore, at least one side effect was reported by 38.2% of participants in the Pharmaceutical Condition and 32.3% of participants in the Natural Condition. Skin irritation was the most commonly endorsed side effect in both conditions (Pharmaceutical Condition: 16.1%, Natural Condition: 13.7%) and headache was the least common (0.6% in both conditions).

3.4. Did we observe placebo effects?

Pain Intensity (MPQ, VAS and OPI) and Pain Tolerance scores for each condition were entered into a repeated-measures ANOVA to determine whether a significant placebo effect was observed.

There was a significant group effect of condition on Pain Intensity (VAS: $F(2, 166) = 7.71$, $p < 0.01$, MPQ: $F(2, 166) = 3.74$, $p < 0.05$) and Pain Tolerance ($F(2, 166) = 5.94$, $p < 0.01$). No significant group effect was observed for OPI Pain Intensity ($F(2, 166) = 2.23$, $p = 0.11$). Post-hoc analyses revealed a significant placebo effect was observed in both the Pharmaceutical and Natural Conditions for VAS Pain Intensity. Similarly, participants were able to tolerate the pain significantly longer in both the placebo conditions compared to the No Placebo Condition. There was no significant difference in Pain Tolerance or VAS Pain Intensity between the Natural and Pharmaceutical Conditions (see Table 5).

Participants reported lower MPQ Pain Intensity when they used the Natural Placebo than when they used No Placebo, but did not when they used the Pharmaceutical Placebo. No significant differences in MPQ Pain Intensity were observed between the Pharmaceutical Condition and the No Placebo Condition or Natural Condition, respectively (see Table 5).

3.5 Hypothesis testing

Sociodemographics had no significant effect on the MPQ, VAS, OPI or Tolerance Placebo Effect and were therefore not included in subsequent analyses.

Hypothesis 1: Variation in placebo responses in both conditions will be predicted by the participant's Necessity beliefs.

Multiple linear regression showed that the MPQ Placebo Effect was significantly positively associated with Specific Necessity beliefs for each treatment (Pharmaceutical: F change (2,168) = 10.75, $p < 0.01$ vs Natural: F change (2,168) = 6.37, $p < 0.05$), confirming Hypothesis 1. Specific Necessity beliefs explained 6.1% (Pharmaceutical) and 6.9% (Natural) of the variation in MPQ Placebo Effect. Participants response increased by 0.25 and 0.19 units per unit increase in Necessity for the Pharmaceutical and Natural Conditions, respectively (see Table 6).

Scores on the Perceived Sensitivity to Medicines Scale (PSM – an aspect of pharmaceutical schema), explained 2.5% of the MPQ Placebo Effect in the Pharmaceutical Condition (F change (2, 168) = 4.17, $p < 0.05$) but not in the Natural Condition ($p > 0.05$). The MPQ Placebo Effect increased by 0.14 units per unit increase in PSM in the Pharmaceutical Condition (see Table 6). No other treatment beliefs were significant predictors of the MPQ Placebo effect or secondary outcome measures in response to the Natural and Pharmaceutical Placebos (all $p > 0.05$).

The effect of Necessity remained significant when Efficacy Expectations were included in the model (Pharmaceutical: F change (2,168) = 8.16, $p < 0.01$ Natural: F change (2,168) = 5.36, $p < 0.05$) Conditions (see Table 6 and Figure 6). Sociodemographics, Trait Anxiety, Depression and Affect also had no significant effect on this relationship (all $p > 0.05$).

Figure 6: Relationship between the MPQ Placebo Effect and (a) Necessity and (b) Necessity while controlling for Efficacy Expectations (95% CI).

Hypothesis 2: High pain catastrophizing will be associated with stronger Necessity beliefs and a larger placebo effect.

Responses to the pharmaceutical and Natural Placebos were predicted by two of the three components of pain catastrophizing: Feelings of Helplessness (Pharmaceutical: F change (2,168) = 18.93, $p < 0.05$: 3% variance explained, Natural: F change (2,168) = 18.93, $p < 0.05$, 2% variance explained) and Magnification of Pain (Pharmaceutical: F change (2,168) = 4.05, $p < 0.05$, 1.5% variance explained, Natural: F change (2,168) = 6.23, $p < 0.05$, 2.6% variance explained, see Table 6). Rumination was not significantly related to MPQ Pain Intensity responses in either placebo condition (all $p > 0.05$). Components of pain catastrophizing were not significantly associated with secondary outcome measures in response to the Natural and Pharmaceutical Placebos (all $p > 0.05$).

As we found that personal need for the placebo cream and two components of pain catastrophizing significantly predicted the MPQ Placebo Effect, we investigated whether Necessity beliefs mediated the relationship between feelings of Helplessness and Magnification of pain, and the MPQ Placebo Effect. Personal need for the placebo partially mediated the effect of Feelings of Helplessness on the MPQ Placebo Effect (Pharmaceutical Condition = Sobel test statistic: 2.26, $p < 0.05$, Natural Condition = Sobel test statistic: 1.99, $p < 0.05$). Personal need for the placebo did not significantly mediate the effect of Magnification of Pain on the MPQ Placebo Effect ($p > 0.05$, see Figure 7 for statistics).

Figure 7: Necessity significantly partially mediated the effect of Helplessness on the MPQ Placebo Effect but not Magnification of pain. Figure shows regression coefficients. * $p < 0.05$, ** $p < 0.01$. PCS = Pain Catastrophizing.

Hypothesis 3: Specific Necessity will be differentially influenced by general pharmaceutical schema and general beliefs about complimentary medicine.

We used Pearson's correlations to test for relationships between Specific Beliefs about the placebo, pharmaceutical schemas (general beliefs about medicines and PSM) and Beliefs about CAM (CAMBI). Pharmaceutical schemas influenced evaluations of the specific placebo treatments. Individuals were more likely to endorse the Necessity of the Pharmaceutical Placebo treatment if they believed that pharmaceutical medicines were intrinsically beneficial. Participants were more likely to reported greater Concerns about potential adverse effects of both the Pharmaceutical and Natural Placebos if they believed that pharmaceuticals are intrinsically harmful (General-Harm) or believed they were particularly sensitive to the effects of medicines (PSM). Perceived need for the Natural

Placebo was not influenced by participants' Pharmaceutical Schema. Finally, those who had more positive Beliefs about CAM were more likely to endorse the Necessity of the Natural Placebo and report greater Concerns about the Pharmaceutical Placebo (see Figure 8 for statistics).

Figure 8: Significant relationships between Specific Beliefs about the Placebo, Pharmaceutical Schemas, CAMBI and Specific Beliefs about the pharmaceutical and Natural Placebos. PSM – Perceived Sensitivity to Medicines, CAMBI – Complementary and Alternative Medicines Beliefs Inventory. * $P < 0.05$, ** $P < 0.01$.

Hypothesis 4: Negative pharmaceutical schema will be associated with more positive beliefs about complementary and natural remedies and preferences for this type of treatment.

A binomial test was used to determine whether there was a significant preference either the Natural or Pharmaceutical Placebo within our sample. There was an overall but non-significant preference for the Natural Placebo (54.49%, $p > 0.05$). Independent t-tests were conducted to determine whether there were significant differences in Treatment Beliefs and Beliefs about CAM between those who would prefer to use the Natural Placebo and those who would prefer to use the Pharmaceutical Placebo in a real health situation. Those who preferred to use the Natural Placebo tended to believe that pharmaceuticals were less beneficial, more intrinsically harmful and overused and had higher PSM than those who preferred to use the Pharmaceutical Placebo. Those who preferred to use the Natural Placebo also had significantly higher Concerns about the Pharmaceutical Placebo and more positive beliefs about CAM than those who preferred to use the Pharmaceutical Placebo (see Table 7 for statistics).

Independent t-tests were conducted to determine whether Pain Intensity in response to each placebo was different for those who preferred the Natural vs. Pharmaceutical Placebo. We found that Pain Intensity in response to the Pharmaceutical Placebo was significantly lower in participants who preferred the Pharmaceutical over the Natural Placebo than vice versa (Pharmaceutical: mean reduction = 0.99, SD = 0.27, Natural: mean reduction = 0.01, SD = 0.42, $t(167) = 1.93$, $p < 0.05$). No significant difference in Pain Intensity was found in response to the Natural Placebo in those who preferred Natural vs Pharmaceutical Placebo ($p > 0.05$).

4. Discussion

This study is the first to show a causal relationship between treatment beliefs and the placebo effect. In a randomised, controlled experiment with cross-over design, we investigated whether pain responses to the cold-pressor task were reduced by two types of sham analgesics (deceptive placebos) described as 'natural' vs pharmaceutical and whether responses were predicated by treatment beliefs.

Placebo responses predicted by treatment beliefs

We assessed two categories of treatments belief: *general* beliefs about the particular types of (sham) treatment (natural vs pharmaceutical) and *specific* beliefs about the (sham) treatment allocated in condition. For the latter, we focussed on treatment Necessity, as an indicator of the value that the participant placed on each particular treatment

Both placebos significantly improved pain tolerance. A reduction in pain intensity was observed in both the pharmaceutical and natural conditions but was only statistically significant for natural. Placebo effects were predicated by specific and general treatment beliefs. Specific Necessity beliefs predicted placebo responses (pain intensity and tolerance) in both natural and pharmaceutical conditions. Placebo effects were also directly, and specifically, influenced by beliefs about personal sensitivity to pharmaceutical medicines. Those who believed themselves to be sensitive to pharmaceuticals reported a greater reduction in pain intensity in the pharmaceutical condition but not in the natural condition.

Observed effects were consistent with theoretical predictions

Our findings were consistent with theoretical predictions (see Figure 1). Participants' beliefs about their personal need for each type of placebo were influenced by more general beliefs about pharmaceuticals and CAM as classes of treatment as predicted by our theoretical model [14]. Participants were more likely to endorse the Necessity of the pharmaceutical placebo, but not the natural placebo, if they believed that pharmaceutical medicines are intrinsically beneficial. Necessity beliefs for the Natural Placebo were influenced by general beliefs about CAM but not by pharmaceutical schema. Those who believed that pharmaceuticals are intrinsically harmful or perceived themselves to be sensitive to medicines had stronger concerns about both the pharmaceutical and natural placebos.

Preference for the Natural Placebo was associated with more negative pharmaceutical schema, greater concerns about the Pharmaceutical Placebo and more positive beliefs about CAM. These findings are consistent with previous studies [2; 9] and theoretical predictions that preferences for specific treatments are influenced by more general perceptions of classes of treatment, which vary between individuals[14; 20]

Also in accordance with theoretical predictions (Figure 1), representations of the problem (feelings of helplessness) influenced representations of the solution (treatment Necessity beliefs) which in turn influenced the placebo effect. Furthermore, we found that the effects of feelings of helplessness on the placebo responses were mediated by Necessity beliefs.

Participants expected the pharmaceutical placebo to be more effective yet the placebos did not differ in their effect on pain perception. However, participants also had more concerns about adverse effects in the pharmaceutical than in the natural condition. This combination of results suggests an interesting constellation of challenges for both types of ‘intervention’. Pharmaceuticals seem to benefit from larger expectations of efficacy which could potentially boost their therapeutic outcome. But this desired effect may be counteracted by heightened concern about adverse effects. This is consistent with observations that pharmaceuticals are often perceived as a ‘double-edged sword’ where therapeutic efficacy goes hand in hand with toxicity [13; 14]. This observation might also help explain our, apparently anomalous, finding that high Necessity beliefs for the pharmaceutical placebo were predicted by beliefs that pharmaceuticals are intrinsically beneficial but also by beliefs that they are intrinsically harmful.

Strategies, to improve the outcome of pharmaceuticals might therefore want to target concerns about potential side effects as well as enhancing prior expectations because highly efficacious medicines may be perceived to be intrinsically more toxic, as their ‘power’ has dual effect: benefit and harm. This idea is supported by the observation that treatment Necessity beliefs and concerns are sometimes positively correlated in clinical samples [3; 15; 18]. The issue seems to be reversed for natural treatments. There is less worry about side effects (which could hinder the therapeutic effect), but a low expectancy level might undermine a positive treatment experience [9].

Beyond expectations

Our findings suggest that placebo effects are susceptible to more complex and diverse beliefs about a treatment than expectations of efficacy alone. In contrast to previous studies [10; 11; 28; 30; 38], we did not find a significant effect of expectations on the placebo effect. This may be a consequence of our experimental design. Usually expectation-focused studies involve directly inducing different expectations of symptom severity after placebo administration [30; 37]. In our study we told participants that both treatments were “highly effective” and participants may therefore have had high expectations of both placebos.

Efficacy expectations are likely to contribute to perceptions of treatment Necessity [14; 19]. For example, a previous study found that 25% of the variance in the perceived need of anti-

retroviral medication was due to efficacy expectations. However, Necessity beliefs are not synonymous with efficacy expectations [14]. We might perceive the need for a treatment that we believe will have only minimal effects because we perceive a personal value in achieving that effect or if it is the only treatment option available. Likewise, we may perceive a treatment to be effective, but, at the same time, to be of low personal value because we are unconvinced of our need for it. In this respect Necessity beliefs can be considered as an indicator of the value that the individual places on the specific treatment [14].

Limitations

Our study had several limitations. Our student sample was highly educated, younger, and possibly healthier than the general population, limiting the generalisability of our findings. There is no definitive protocol for the cold pressor paradigm leading to variations in equipment and water temperature that may influence results across studies. Furthermore, habituation, audience, and demand effects are all known to influence pain and tolerance [12; 25; 39; 42; 43]. We minimised these effects by conducting the experiment in a private room, keeping the experimenter, information and instructions to participants constant, and keeping the temperature of our water bath constant within $\pm 0.03^{\circ}\text{C}$. We minimised the effect of habituation on our results by randomising both condition order and hand order. Although we did observe significant order effects for the natural condition but not in the pharmaceutical condition, our results were as predicted in both conditions. We suspect that this effect represents some degree of habituation; however, this did not influence our results. We also allowed time between conditions for participants' hands to reacclimatise to room temperature.

We did not observe a significant placebo effect in response to every pain measure. For example, we found no significant MPQ Placebo Effect in the Pharmaceutical Condition but did in the Natural Condition. However, our analyses were still able to predict which participants would report a larger placebo effect based on their beliefs about each placebo. We conducted a manipulation check at the end of our experiment to ensure that our results were not simply due to demand effects. The majority of our sample believed that both pain relieving creams were active medications. A third of our sample reported a side effect which supports that the placebo cream was convincing as a drug. The study had several strengths. We recruited a large sample size and employed a within subject design, thus maximising statistical power and reducing error variance associated with individual differences. Pain Intensity scores were similar to the magnitude of pain in a number of untreated clinical pain conditions [8; 29; 41]. Differences between Pain Intensity and Tolerance in the No Placebo

Condition and in both Placebo Conditions were also similar to previous studies investigating the placebo effect using the cold pressor task [6; 28; 33].

Conclusion

Despite its limitations, this study demonstrated that placebo effects were influenced by specific and general treatment beliefs in a way that was consistent with theory. Participants differed in their background beliefs about pharmaceutical and natural treatments and perceptions self in relation to medicines (personal sensitivity to medicines). Pharmaceutical schema influenced their evaluation of specific pharmaceutical and natural (sham) treatments and their beliefs in the necessity of the treatment for reducing pain, which in turn, influenced pain responses. Our findings suggest that beliefs about treatment may offer an additional approach for studying placebo effects. Further studies are now justified to explore these issues in more detail to assess further the value of treatment beliefs in understanding placebo effects.

Our findings might also stimulate research in clinical samples. A proportion of the outcome of active treatments is explained by non-specific effects placebo effects exist when taking active medications [4]. Furthermore, there is evidence that treatment beliefs influence side effect reporting [1; 17; 26]. The treatment beliefs we studied have previously been shown to influence adherence to medicines in numerous studies [15]. It may be that interventions that to support adherence by influencing these beliefs might also have a direct effect on treatment outcome.

6. Conflict of interest statement

The authors declare no relevant conflicts of interest

7. References

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Table 1: Modified items of the BMQ-S scales

Necessity	Concerns
This cream is necessary to reduce my pain	Using this cream worries me
I would experience more severe pain without this cream	I am concerned about the long-term effects of this cream
Using this cream makes me less anxious about the pain in this study	How this cream works is a mystery to me
This pain relieving cream will protect me from feeling pain	I am concerned that this cream won't work
	I am concerned that this cream might cause a side effect
	I am concerned this cream will affect my sense of touch in my hand
	It would worry me to feel as though I depended on this cream to tolerate the pain

Note: BMQ-S = Beliefs about Medicines Questionnaire - Specific

Table 2: Demographics

	Mean (SD)
Age (years)	25.69 (8.40)
	n (%)
Female	107 (63.70%)
Currently studying:	
Undergraduate degree	59 (35.10%)
Postgraduate degree	93 (64.90%)
Ethnicity	
White British/American/European	92 (54.80%)
Other	75 (45.20%)
First Language	
English	100 (59.52%)
Other	64 (40.47%)

Table 3: Baseline measures

	Mean (SD)
General Benefit	3.98 (0.45)
General Harm	2.24 (0.59)
General Overuse	3.06 (0.69)
PSM	2.05 (0.58)
CAMBI - Natural Treatment	17.45 (4.51)
CAMBI - Holistic Treatment	20.65 (3.86)
CAMBI - Holistic Health	15.38 (3.81)
Trait Anxiety	43.18 (6.49)
PCS - Rumination	5.24 (3.90)
PCS - Magnification	2.43 (1.99)
PCS - Helplessness	4.90 (3.98)
	Median (IQR)
Depression	3.00 (6.00)

Note: PSM – Perceived Sensitivity to Medicines Scale, CAMBI – Complementary and Alternative Medicines Belief Inventory, PCS – Pain Catastrophizing Scale

Table 4: Comparison of Specific Beliefs, Expected Pain Intensity and Expected Efficacy across conditions

	Condition Mean (SD)			p
	No Placebo	Pharmaceutical	Natural	
Necessity	--	3.35 (0.57)	3.16 (0.6)	<0.001
Concerns	--	2.64 (0.62)	2.44 (0.55)	<0.001
Expected Efficacy	--	64.82 (16.60)	57.88 (16.60)	<0.01
Expected Pain Intensity	67.08 (21.41)	47.07 (18.21)	50.21 (20.54)	<0.001 ^{a,b}

Note: p values relate to paired t-tests. a = No Placebo – Pharmaceutical Condition, b = No Placebo – Natural Condition.

Table 5: Comparison of Pain Intensity and Pain Tolerance across conditions

	Condition Mean (SD)			p
	No Placebo	Pharmaceutical	Natural	
Pain Intensity:				
MPQ	14.23 (8.32)	13.61 (7.73)	12.97 (7.51)	<0.05 ^b
VAS	69.79 (18.68)	65.09 (18.21)	63.52 (19.68)	<0.05 ^a , <0.001 ^b
PPI	3.75 (0.96)	3.64 (0.84)	3.56 (0.89)	<0.01 ^b
Pain Tolerance (seconds)	55.07 (44.32)	61.63 (43.73)	63.63 (43.09)	<0.05 ^a , <0.05 ^b

Note: VAS = Visual Analogue Scale, MPQ = McGill Pain Questionnaire, PPI = Present Pain Intensity. p values refer to the results of repeated-measures ANOVA post-hoc test (Bonferroni). Statistical comparisons - a = No Placebo - Pharmaceutical, b = No Placebo - Natural, c = Pharmaceutical - Natural

Table 6: The effect of a) Necessity b) Necessity while controlling for Efficacy Expectations c) PSM and d) Magnification of Pain and feelings of Helplessness on the MPQ Placebo Effect.

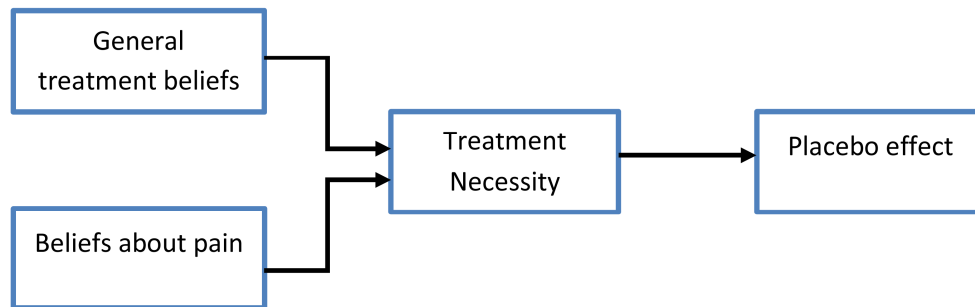
Model	Condition			
	Pharmaceutical		Natural	
	B [95% CI]	p	B [95% CI]	p
a)				
<i>Baseline:</i>				
Constant	0.91 [0.67, 1.14]	<0.001	0.59 [0.36, 0.81]	<0.001
Condition order	0.01 [-0.01, 0.01]	>0.05	0.01 [0, 0.01]	<0.05
<i>Model 1: Baseline plus -</i>				
Necessity	0.22 [0.09, 0.35]	<0.01	0.16 [0.04, 0.28]	<0.05
b)				
<i>Baseline:</i>				
Constant	0.71 [0.37, 1.05]	<0.001	0.50 [0.22, 0.78]	<0.01
Condition order	0.01 [-0.01, 0.01]	>0.05	0.01 [0, 0.01]	<0.05
Efficacy Expectation	0.01 [-0.01, 0.01]	>0.05	0.01 [-0.01, 0.01]	>0.05
<i>Model 1: Baseline plus -</i>				
Necessity	0.21 [0.06, 0.35]	<0.01	0.16 [0.02, 0.29]	<0.05
c)				
<i>Baseline:</i>				
Constant	0.91 [7.60, 0.01]	<0.001	-	-
Condition order	0.01 [0.05, 0.96]	>0.05	-	-
<i>Model 1: Baseline plus -</i>				
PSM	0.14 [2.04, 0.43]	<0.05	-	-
d)				
<i>Baseline:</i>				
Constant	0.91 [0.67, 1.14]	<0.001	0.59 [0.36, 0.81]	<0.001
Condition order	0.01 [-0.01, 0.01]	>0.05	0.01 [0, 0.01]	<0.05
<i>Model 1: Baseline plus-</i>				
PCS: Magnification	0.04 [0.01, 0.08]	<0.05	0.05 [0.01, 0.09]	<0.05
<i>Model 2: Baseline plus-</i>				
PCS: Helplessness	0.03 [0.1, 0.05]	<0.01	0.02 [0.01, 0.04]	<0.05

Note: MPQ = McGill Pain Questionnaire, PCS = Pain Catastrophizing Scale, PSM, Perceived Sensitivity to Medicines

Table 7: Comparison of Treatment Beliefs and beliefs about CAM between those who preferred to use the Pharmaceutical vs. Natural Placebo.

	Preference for: (Mean (SD))		p
	Pharmaceutical Placebo	Natural Placebo	
General Benefit	4.08 (0.39)	3.90 (0.48)	< 0.01
General Harm	2.08 (0.58)	2.54 (0.56)	<0.001
General Overuse	2.97 (0.70)	3.38 (0.71)	<0.001
PSM	1.89 (0.53)	2.18 (0.59)	<0.01
Pharmaceutical Placebo : Necessity	3.41 (0.53)	3.30 (0.65)	>0.05
Pharmaceutical Placebo : Concerns	2.45 (0.53)	2.81 (0.61)	<0.001
Natural Placebo: Necessity	3.12 (0.59)	3.19 (0.61)	>0.05
Natural Placebo: Concerns	2.37 (0.51)	2.50 (0.57)	>0.05
CAMBI: Holistic Health	14.50 (3.70)	16.18 (3.76)	<0.01
CAMBI: Holistic Treatment	19.70 (3.76)	21.45 (3.78)	<0.01
CAMBI: Natural Treatment	15.73 (4.11)	18.91 (4.34)	<0.001

Note: PSM = Perceived Sensitivity to Medicines, CAMBI = Complementary and Alternative Medicines Belief Inventory

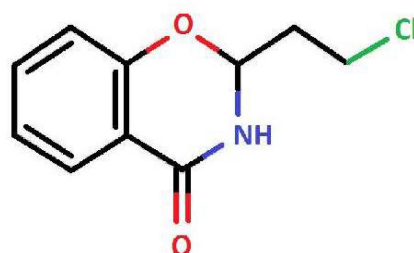


Xyloptan[®]

PAIN-RELIEVING CREAM INFORMATION

1. WHAT IS XYLOPTAN AND HOW DOES IT WORK?

Xyloptan is a pharmaceutical cream used to prevent and relieve pain. Its active ingredient, chlorthenoxazine was first synthesised in the laboratory over 40 years ago. It has undergone further development and testing and is licenced for use as Xyloptan pain-relieving cream, which is marketed by an international pharmaceutical company. Studies have shown this medicine to be highly effective in reducing the type of pain you're about to experience. It works within the central nervous system, reducing pain perception within the brain.



Chlorthenoxazine

- Chemical formula: $C_{10}H_{10}ClNO_2$
- Molecular weight: 211
- Therapeutic category: Analgesic agent

2. BEFORE YOU USE XYLOPTAN

This cream should **not** be used on the following areas:

- Cuts, grazes or wounds.
- Where there is a skin rash or eczema.
- In or near the eyes.
- Inside the nose, ear or mouth.

3. HOW TO USE XYLOPTAN

In this study, we will ask you to apply this cream to the back of your hand (while wearing a glove on the hand you use to apply the cream). Gently massage the cream into your skin. You may experience a slight tingling on your hand when it takes effect.

Cassibalm[®]

PAIN-RELIEVING CREAM INFORMATION

1. WHAT IS CASSIBALM AND HOW DOES IT WORK?

Cassibalm is a natural remedy used to prevent and relieve pain. It contains oils extracted from the seeds of the *Cassia occidentalis* plant. This plant is found in the Amazon and has been used by indigenous people to reduce pain for centuries. Studies have shown this cream to be highly effective in reducing the type of pain you are about to experience. The cream works by triggering the body's natural pain reducing processes (endorphins).



Cassia occidentalis

- Commonly known as Fedegoso
- Grows 5-8m high
- Related to the species *Senna*, which is also used as a natural remedy for pain

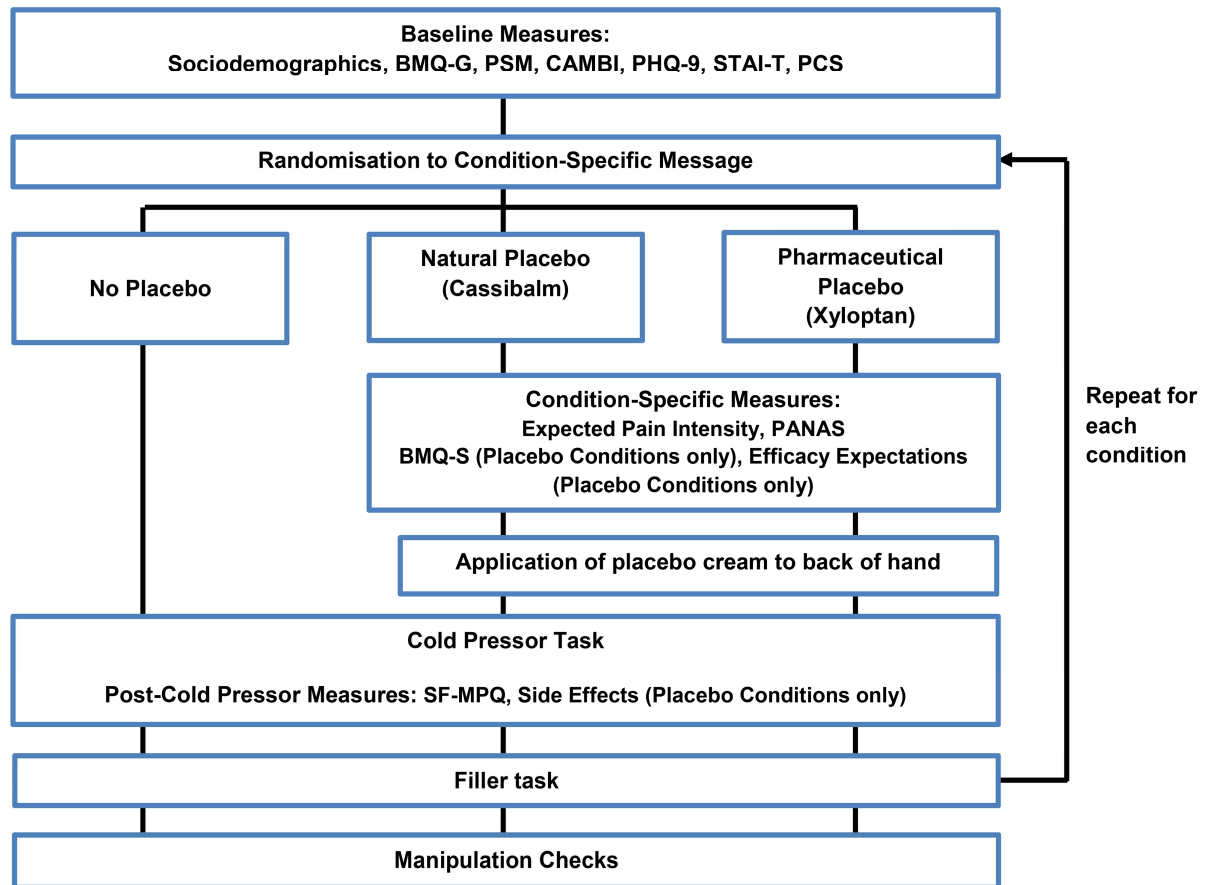
2. BEFORE YOU USE CASSIBALM

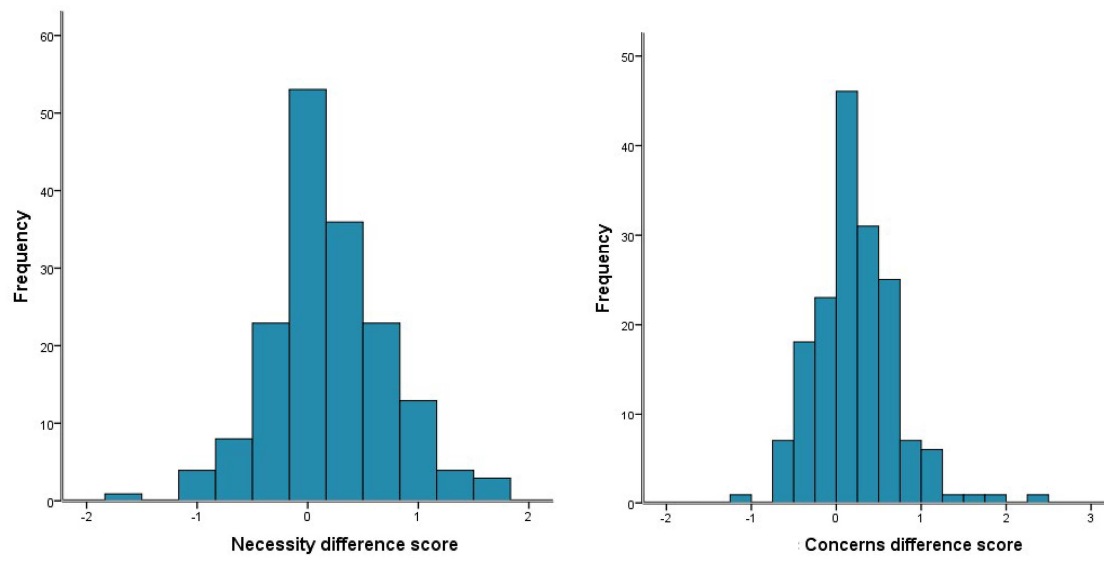
This cream should **not** be used on the following areas:

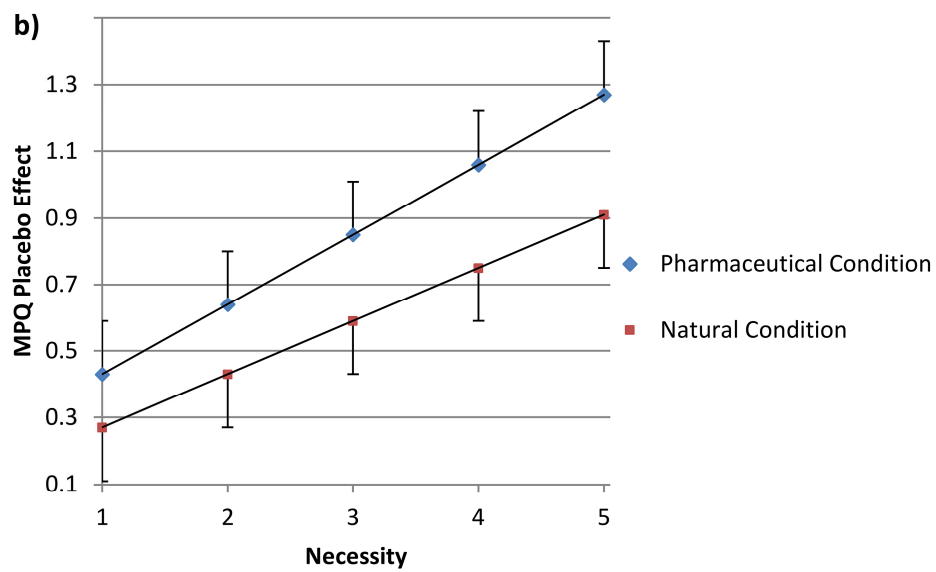
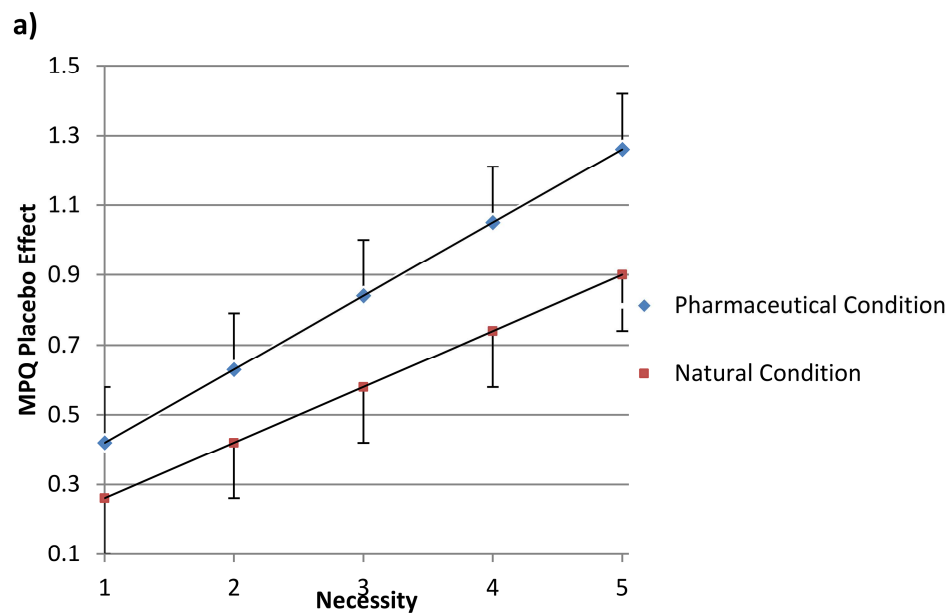
- Cuts, grazes or wounds.
- Where there is a skin rash or eczema.
- In or near the eyes.
- Inside the nose, ear or mouth.

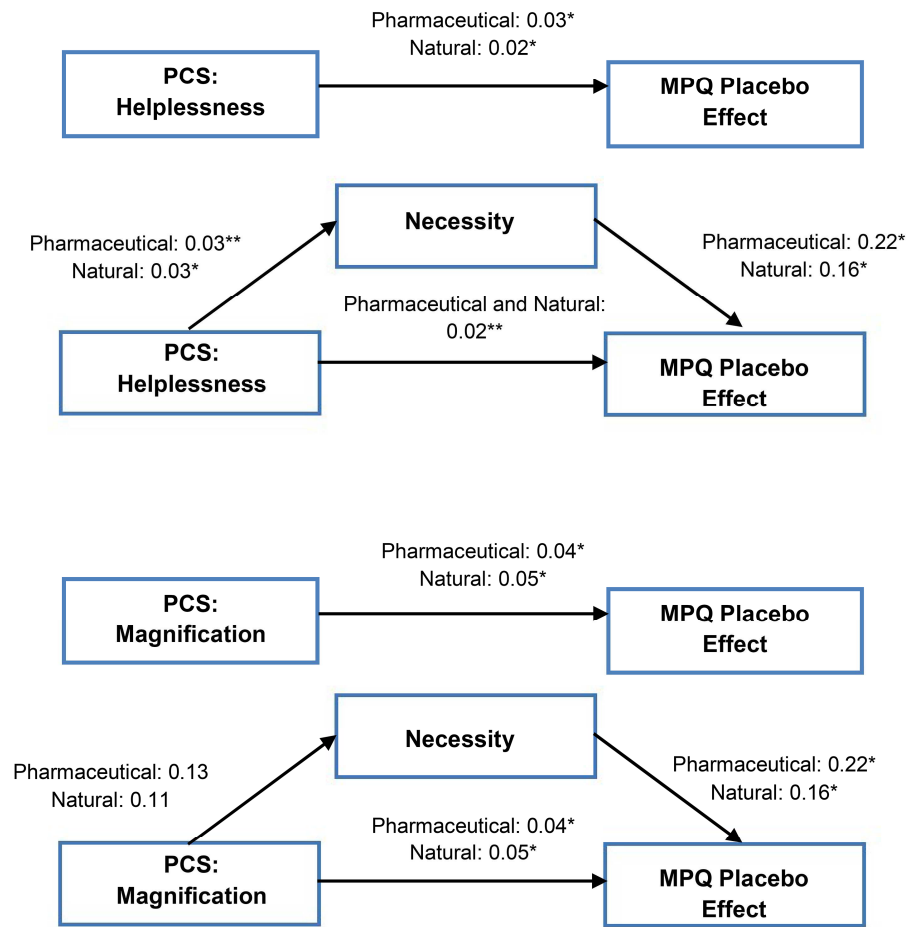
3. HOW TO USE CASSIBALM

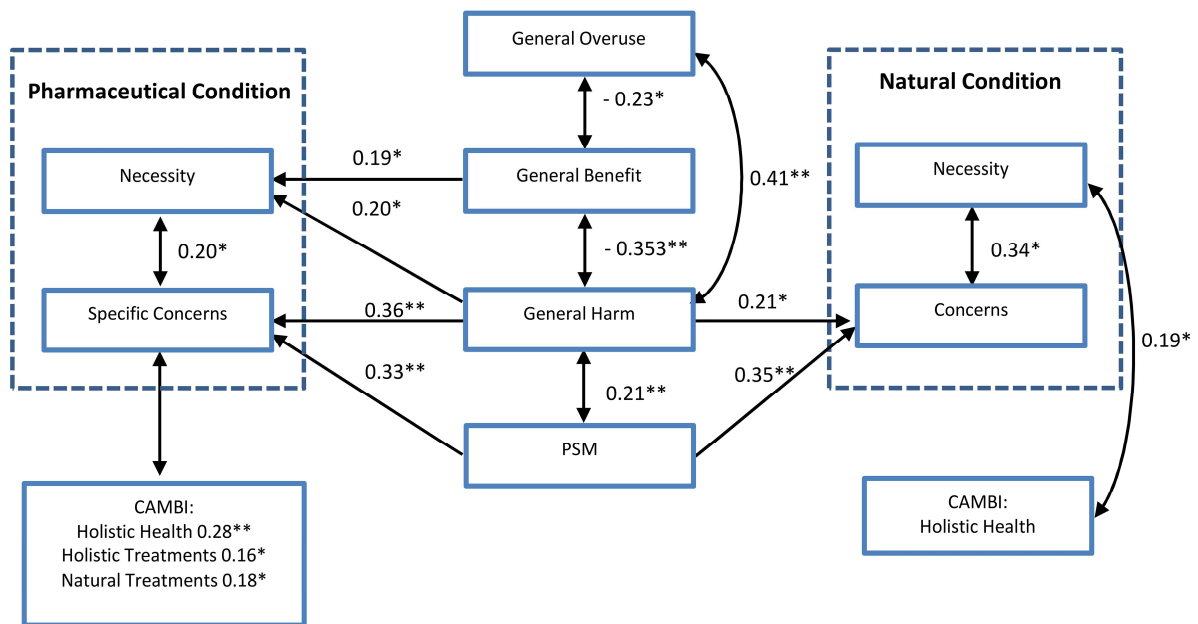
In this study, we will ask you to apply the cream to the back of your hand (while wearing a glove on the hand you use to apply the cream). Gently massage the cream into your skin. You may experience a slight tingling on your hand when it takes effect.











Highlights

Treatment beliefs offer an additional approach to understanding placebo analgesia

Variation in placebo analgesia was predicted by pre-treatment necessity beliefs

Treatment necessity beliefs were informed by general treatment beliefs and beliefs about the pain

Perceived sensitivity to the effects of medicines was associated with larger placebo analgesia